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(54) **Aminobutyronitrile compositions**

(57) There is provided a stable optically active composition comprising up to about 65% by weight of (R)-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent. Said composition is useful in the manufacture of agriculturally active agents.

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Description

BACKGROUND OF THE INVENTION

5 [0001] Phenoxypropionic acid cyanimide derivatives, such as those described in EP 262,393 and Research Disclosure 92306005, are useful as fungicides, particularly for the control of the causative agents of rice blast. Said cyanimide derivatives contain assymetric or stereogenic carbon atoms and it has been demonstrated that those derivatives having the R-configuration show enhanced fungicidal activity over that of the corresponding racemic mixtures. Similarly, the imidazolinone family of herbicides, such as those described in U.S. 4,798,619 and U.S. 5,334,576, contain assymetric or stereogenic carbon atoms and it has been demonstrated that those imidazolinones having the R-configuration on the dialkylsubstituted carbon atom in the imidazolinone ring show a greater herbicidal activity than the corresponding racemic mixtures.

10 [0002] A common key chiral intermediate compound, (R)2-amino-2,3-butyronitrile may be used to prepare the above-said agriculturally active compounds. However, said (R)aminobutyronitrile compound is unstable and readily racemizes upon standing, thus making practical manufacturing procedures difficult.

15 [0003] Therefore, it is an object of this invention to provide a stable (R)2-amino-2,3-dimethylbutyronitrile composition useful for the manufacture of agriculturally active compounds.

[0004] It is another object of this invention to provide a readily available, storage-stable source of (R)2-amino-2,3-dimethylbutyronitrile.

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SUMMARY OF THE INVENTION

[0005] The present invention provides a stable chiral composition which comprises up to about 65% by weight of (R)2-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent. Said compositions are useful as intermediates in the manufacture of agriculturally active agents such as fungicidal cyanimides and herbicidal imidazolinones having the R-configuration.

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DETAILED DESCRIPTION OF THE INVENTION

30 [0006] Fungicidal α -phenoxypropionic acid cyanimide derivatives and their preparation from (R)2-amino-2,3-dimethylbutyronitrile are described in Research Disclosure 92306005. Herbicidal imidazolinones and their preparation from (R)2-amino-2,3-dimethylbutyronitrile are described in U.S. 4,683,324. Said patent also describes the preparation and isolation of (R)2-amino-2,3-dimethylbutyronitrile. Although said (R)aminobutyronitrile may be potentially useful as a key common intermediate in the manufacture of agriculturally active agents such as fungicides and herbicides, its half-life is estimated to be less than 8 hours at room temperature, therefore, making its use in a manufacturing procedure highly impractical.

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[0007] Surprisingly, it has now been found that a composition which comprises up to about 65%, preferably 5% to 65%, more preferably 5% to 50%, especially preferably 15% to 40%, by weight of (R)2-amino-2,3-dimethylbutyronitrile (hereinafter designated R-aminonitrile) and a substantially water-free non-polar solvent is storage-stable for prolonged periods of time at temperatures at or below room temperature (up to about 25°C). Higher temperatures or higher concentrations may be employed, in the inventive compositions, however higher temperatures or higher concentrations accelerate the racemization process while lower temperatures or lower concentrations decrease the rate of racemization and increase the storage-stable period of time.

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[0008] Advantageously, the composition of the invention may be employed in a practical manufacturing procedure, such as a process to prepare fungicidal α -phenoxycyanimides or herbicidal imidazolinones having the R configuration, without rapid decomposition due to racemization or loss of HCN from the R-aminonitrile starting material. Further, the stability of the composition of the invention allows for interim storage or transportation of the R-aminonitrile compound as needed for manufacturing purposes. It is intended that the stable chiral aminobutyronitrile compositions of the invention also embrace the corresponding essentially enantiomerically pure (S)2-amino-2,3-dimethylbutyronitrile compound as the chiral component therein.

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[0009] Non-polar solvents useful in the composition of the invention are aromatic hydrocarbons (e.g. toluene, benzene, xylene, naphthalene and the like preferably toluene), halogenated aromatic hydrocarbons (e.g. chlorobenzene, dichlorobenzenes and the like), hydrocarbons (e.g. pentanes, hexanes and the like), halogenated hydrocarbons (e.g. chloroform, methylene chloride, dichloroethane, and the like, esters (e.g. ethyl acetate, methyl propionate and the like), ethers (e.g. diethyl ether, tetrahydrofuran, dioxane and the like) or any of the conventional, preferably water immiscible, organic non-polar solvents.

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[0010] Preferred non-polar solvents suitable for the composition of the invention are aromatic hydrocarbons, particularly toluene.

[0011] In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating certain more specific details thereof. The invention is not to be deemed limited thereby except as defined in the claims.

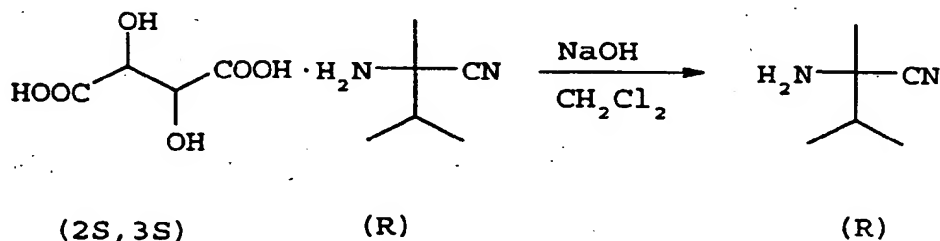
[0012] Unless otherwise noted, all parts are parts by weight. HPLC designates high performance liquid chromatography.

EXAMPLE 1

Evaluation Of The Solvent Effect On The Racemization Of A 10% Solution of (R)2-Amino-2,3-dimethylbutyronitrile

A) Preparation of (R)2-Amino-2,3-dimethylbutyronitrile

[0013]



[0014] A mixture of methylene chloride, ice, (R)2-amino-2,3-dimethylbutyronitrile (2S,3S) tartaric acid salt (8.13g, 31.0 mmol) and 50% NaOH (5.3 ml, 8.0 g, 100 mmol NaOH) is shaken until no solid particles are observed. The organic phase is separated, dried over MgSO_4 and filtered. The filtrate is distilled *in vacuo* at 20°C to remove the methylene chloride and obtain free (R)2-amino-2,3-dimethylbutyronitrile as a clear liquid, 3.42 g (98.3% yield).

B) Optical Rotation Evaluation

[0015] In these evaluations, 10% wt/wt solutions of the freshly prepared (R)2-amino-2,3-dimethylbutyronitrile in a variety of solvents are placed in a constant temperature bath. Optical rotations, $([\alpha]_D)$ are determined at time 0 and at regular intervals thereafter. The data obtained are shown in Tables I and II.

Table I

Evaluation of Non-polar Solvent Effect On Stability Of (R)2-
Amino,2,3-dimethylbutronitrile Compositions

<u>Solvent</u>	<u>Time (Hr.)</u>	<u>$[\alpha]_D$</u>	<u>$\Delta^1 [\alpha]_D$</u>	<u>Temperature (°C)</u>
Ethyl Acetate	0	-00.422		26
	1	-00.422		26
	2.5	-00.425		26
	3.5	-00.424	-0.002	26
	4.5	-00.424		26
	19.5	-00.421		26
		-00.423		26
Toluene	0	-00.423		26
	1	-00.423		26
	2	-00.423		26
	7	-00.423	0.000	26
	23	-00.423		26
Acetonitrile	0	-00.209		26
	1	-00.204		26
	2	-00.199		26
	3	-00.197	0.012	26
	312	-00.025		26

	<u>Solvent</u>	<u>Time (Hr.)</u>	<u>$[\alpha]_D$</u>	<u>$\Delta' [\alpha]_D$</u>	<u>Temperature (°C)</u>
5					
	Tetrahydrofuran	0	-00.520		26
		1	-00.520		26
10		2	-00.518		26
		4.5	-00.518	0.002	26
15		27	-00.515		26
	Methylene Chloride	0	-00.468		26
20		1	-00.467		26
		2	-00.461	0.007	26
		17.5	-00.458		26
25					
	Chloroform	0	-00.547		26
		1	-00.549		26
30		2	-00.547	0.000	26
		17.5	-00.540		26
35					
	Dimethyl Formamide	0	-00.081		26
		1	-00.074		26
		3	-00.062	0.019	26
40		23	-00.015		26
		168	+00.002		26
45					
50					
55					

	<u>Solvent</u>	<u>Time (Hr.)</u>	<u>$[\alpha]_D$</u>	<u>$\Delta^t [\alpha]_D$</u>	<u>Temperature (°C)</u>
5	Ethyl Ether	0	-00.505		26
		1	-00.505		26
10		4	-00.502	0.003	26
		6	-00.504		26
15	Hexanes	0	-00.492		26
		1	-00.494		26
		4	-00.491	0.001	26
20		6	-00.482		26
	Chlorobenzene	0	-00.306		25
25		1	-00.304		25
		3	-00.289	0.017	25
30		20.5	-00.285		25
	o-Dichlorobenzene	0	-00.242		25
		1	-00.241		25
35		3	-00.240	0.002	25
		20.5	-00.229		25
40	Nitrobenzene	0	-00.068		25
		1	-00.051		25
45		3	-00.045	0.023	25
		20.5	-00.053		25

Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta' [\alpha]_D$	Temperature (°C)
1,2-Dichloroethane	0	-00.419		25
	2	-00.408		25
	4	-00.421	-0.002	25
	6	-00.436		25
1,2-Dimethoxyethane	0	-00.493		25
	2	-00.494		25
	4	-00.508	-0.015	25
	6	-00.514		25
2-Butanone	0	-00.368		25
	2	-00.366		25
	4	-00.358	0.014	25
	6	-00.357		25
Xylenes	0	-00.447		25
	2	-00.442		25
	4	-00.453	-0.006	25
	6	-00.460		25

$\Delta' [\alpha]_D = [\alpha]_D$ at Time 0 minus $[\alpha]_D$ at Time T

Table II

Comparative Evaluation of Polar Solvent Effect On Stability Of (R)2-Amino,2,3-dimethylbutronitrile Compositions				
Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta^1 [\alpha]_D$	Temperature (°C)
Methanol	0	-00.500	0.485	26
	1	-00.173		27
	2	-00.054		27
	3	-00.015		26
(±)2-Butanol	0	-00.541	0.311	26
	1	-00.425		26
	2	-00.359		26
	4.5	-00.230		26
	27	-00.000		26
Dimethylsulfoxide	0	-00.239	0.180	26
	1	-00.151		26
	3	-00.059		26
	23	+00.003		26
	168	-00.003		26
Ethanol	0	-00.540	0.476	26
	1	-00.298		26
	2	-00.145		26
	4	-00.064		26
	6	-00.022		26

$$^1 \Delta [\alpha]_D = [\alpha]_D \text{ at Time 0 minus } [\alpha]_D \text{ at Time T}$$

As can be seen from the data shown in Tables I and II above, racemization is decreased by a factor of 10 to 100 fold when the chiral compound is present as a 10% solution in a non-polar solvent as compared to when it is present as a 10% solution in a polar solvent.

EXAMPLE 2

Comparative Evaluation Of The Effect Of Water On The Racemization Of A Toluene Solution Of (R)2-Amino-2,3-dimethylbutyronitrile

[0016] In this evaluation, (R)2-amino-2,3-dimethylbutyronitrile is prepared in a manner similar to that described in part A of Example 1 and employing toluene in place of methylene chloride. Upon extraction and separation, a 25.8% solution of free 2-amino-2,3-dimethylbutyronitrile in toluene is obtained. Immediately after extraction, the % R isomer of the water wet toluene solution is determined by HPLC analysis. The wet solution is stored at 25°C for 24 hours and a second measurement is taken. The wet solution is then dried azeotropically (45°-50°C/60-65 mmHg), analyzed for % R isomer by chiral HPLC immediately after drying, stored at 25°C for 4 days and analyzed a second time. The results are shown in Table III.

Table III

Comparative Evaluation Of The Effect Of Water On The Stability Of (R)2-Amino,2,3-dimethylbutronitrile Compositions			
Solvent	Time (Days)	% R Isomer	$\Delta\% R^1$
Wet Toluene (comparison)	0	85.2	
Wet Toluene (comparison)	1	80.3	-4.9
Dry Toluene (invention)	0	79.5	
Dry Toluene (invention)	4	78.9	-0.6

¹ $\Delta\%R = \% R$ at Time 0 minus $\% R$ at Time T

As can be seen from the data in Table III above, solutions of the chiral compound in essentially the absence of water are significantly more stable than those solutions in which water is present.

EXAMPLE 3

Evaluation Of The Effect Of Temperature And Concentration On The Racemization Of A Solution of (R)2-Amino-2,3-dimethylbutyronitrile

[0017] In these evaluations, the test solution is prepared in essentially the same manner as described in Example 2 and the solution is azeotropically dried immediately following extraction. A 50 g sample of the thus-prepared test solution is introduced into a 3-necked round bottom flask which has been set at a predetermined temperature and flushed with nitrogen. Samples of the test solution are taken directly from the flask at 0, 4, 24 and 48 hour intervals and analyzed for % R isomer and wt % concentration of (R,S)2-amino-2,3-dimethylbutyronitrile by chiral HPLC. The data obtained are shown in Table IV.

Table IV

**Evaluation of The Effect Of Concentration And Temperature On the Stability Of
(R)2-Amino,2,3-dimethylbutyronitrile Compositions**

Concentration (wt %)	Temperature (°C)	Time (Hr.)	%R Isomer	$\Delta\% R^1$
19.2	15	0	94.0	
19.5	15	4	93.9	
19.4	15	24	93.9	
19.2	15	48	93.6	0.4
19.2	20	0	94.2	
19.2	20	24	94.0	
19.2	20	48	94.0	0.2
19.2	60	0	94.0	
19.5	60	4	91.9	
19.8	60	24	81.6	
20.2	60	48	71.6	22.4
32.2	20	0	93.5	
32.2	20	48	93.1	0.4
38.6	2	0	93.4	
37.2	2	144	92.9	0.5
38.7	2	336	91.7	
38.6	35	0	93.4	
39.0	35	24	86.9	
38.1	35	48	84.1	9.3
38.3	20	0	90.5	
38.3	20	24	89.5	

¹ $\Delta\%R = \%R$ at Time 0 minus $\%R$ at 48 hr.

Table IV

Concentration (wt %)	Temperature (°C)	Time (Hr.)	%R Isomer	$\Delta\% R^1$
37.2	35	0	92.9	8.6
36.8	35	4	91.4	
36.8	35	24	88.4	
39.2	35	48	84.3	
45.9	45	0	94.4	
46.5	47	2	89.4	
65.2	15	0	92.8	2.9
63.8	15	4	92.6	
64.9	15	24	90.8	
63.4	15	48	89.9	
65.2	60	0	92.8	
64.4	60	4	71.3	
63.4	60	24	51.4	42.4
66.0	60	48	50.5	

¹ $\Delta\%R = \%R$ at Time 0 minus $\%R$ at 48 hr.

As can be seen from the data shown in Table IV above, high concentration combined with high temperature decreases the stability of the chiral solution, however concentrations as high as 65% may be stable at moderate temperature.

Claims

1. A stable composition which comprises up to about 65% by weight of (R)2-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent.
2. The composition according to claim 1 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 65% by weight.
3. The composition according to claim 1 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 50% by weight.
4. The composition according to claim 1 wherein the solvent is selected from the group consisting of aromatic hydrocarbons, halogenated aromatic hydrocarbons, hydrocarbons, halogenated hydrocarbons, esters and ethers.
5. The composition according to claim 4 wherein the solvent is an aromatic hydrocarbon.
6. The composition according to claim 5 wherein the solvent is toluene.
7. The composition according to claim 6 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 65% by weight.
8. The composition according to claim 7 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 15% to 40% by weight.

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EUROPEAN SEARCH REPORT

Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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			C07C C08K A01N
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 16 May 2001	Examiner Bader, K
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**ANNEX TO THE EUROPEAN SEARCH REPORT
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